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Approaches to Evaluating UX007 (Triheptanoin) in Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS)

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Disclaimer

- Dr. Bowden is an Associate Director, Clinical Outcomes Research and Evaluation employed by Ultragenyx Pharmaceutical

Objectives

1. Incorporating the patient perspective in understanding the symptoms and functional impact of Glut1 DS
2. Using qualitative evidence to support the selection/development of meaningful clinical outcome assessments (COAs) for paroxysmal manifestations of Glut1 DS

Topics

- Review of Clinical Outcome Assessments (COAs)
- Understanding Glut1 DS: Qualitative Research
  - Literature review
  - Physician interviews
  - Patient/Caregiver (CG) interviews
  - Patient functional assessment study
- Meaningful COAs for Glut1 DS

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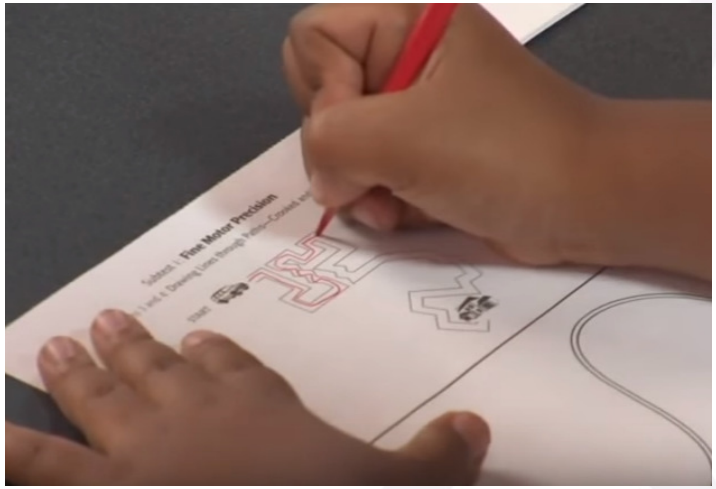
Clinical Outcome Assessments

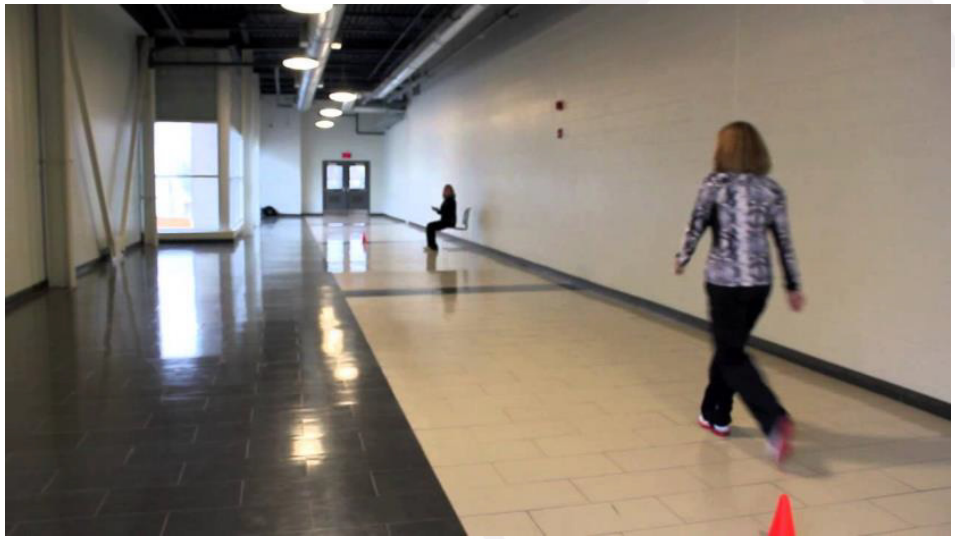
What is a Clinical Outcome Assessment?

- Measure of how a patient survives, feels or functions
  - Determine if a drug has been demonstrated to provide a treatment benefit
- Types of Clinical Outcome Assessments
  - Performance Outcomes (PerfO)
  - Patient-Reported Outcome (PRO)
  - Observer-Reported Outcome (ObsRO)
  - Clinician-Reported Outcome (ClinRO)
- Selecting and Developing Clinical Outcome Assessments
  - Use existing measures
  - Modify existing measures
  - Develop novel measures

Performance Outcome (PerfO)

- Measurement based on a task(s) performed by the patient
- Represent an aspect of daily life that is important to the patient
- Requires cooperation and motivation





Patient Reported Outcome (PRO)

- Report of a patient's health condition that comes directly from the patient
  - Symptom severity e.g. pain
  - Perception of daily functioning
  - Feelings of well being
  - Impact/Satisfaction with treatment
  - Health-Related Quality of Life

Source: http://www.ispor.org/meetings/va0502/symposium.asp

Observer Reported Outcome (ObsRO)

- Measurement based on observation by someone other than the patient or clinician e.g. parent or partner
- For patients that are unable to self report
  - Young children or cognitively impaired
- Report of signs/impacts that are reliably detected
  - Seizure frequency
  - Crying episodes
  - Cough
  - Activity level

Clinician Reported Outcome (ClinRO)

- Involves clinical judgement/ interpretation of the condition
- Rated by a trained health-care professional based on observation/interview
- Unable to assess symptoms known only to the patient
  - Useful when patient unable to self-report
  - Patient unable to comment on a specific sign

Scale for the assessment and rating of ataxia (SARA)

1) Gait	2) Stance
Proband is asked (1) to walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support.	Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other) and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are open. For each condition, three trials are allowed. Best trial is rated.
0 Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed) 1 Slight difficulties, only visible when walking 10 consecutive steps in tandem 2 Clearly abnormal, tandem walking > 10 steps not possible 3 Considerable staggering, difficulties in half-turn, but without support 4 Marked staggering, intermittent support of the wall required 5 Severe staggering, permanent support of one stick or light support by one arm required 6 Walking > 10 m only with strong support (two special sticks or stroller or accompanying person) 7 Walking < 10 m only with strong support (two special sticks or stroller or accompanying person) 8 Unable to walk, even supported	0 Normal, able to stand in tandem for > 10 s 1 Able to stand with feet together without sway, but not in tandem for > 10s 2 Able to stand with feet together for > 10 s, but only with sway 3 Able to stand for > 10 s without support in natural position, but not with feet together 4 Able to stand for >10 s in natural position only with intermittent support 5 Able to stand >10 s in natural position only with constant support of one arm 6 Unable to stand for >10 seven with constant support of one arm
Score	Score
3) Sitting	**4) Speech disturbance**
Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front.	Speech is assessed during normal conversation.
0 Normal, no difficulties sitting >10 sec 1 Slight difficulties, intermittent sway 2 Constant sway, but able to sit > 10 s without support 3 Able to sit for > 10 s only with intermittent support 4 Unable to sit for >10 s without continuous support	0 Normal 1 Suggestion of speech disturbance 2 Impaired speech, but easy to understand 3 Occasional words difficult to understand 4 Many words difficult to understand 5 Only single words understandable 6 Speech unintelligible / anarthria
Score	Score

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Understanding Glut1 DS

Symptoms and Functional Impact

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How do we learn about Glut1 DS?

- Literature review
  - Heterogeneous and complex in symptom presentation
  - Spectrum of paroxysmal manifestations is broad
  - Seizure type and movement disorders are well described
  - Limited information about functional impact in medical literature
- Clinician interviews
- Patient and Caregiver perspective
  - Concept elicitation
    - Patient experience in their own words
  - Evaluation/Observation study

Clinician Interviews[1]: Movement Disorders

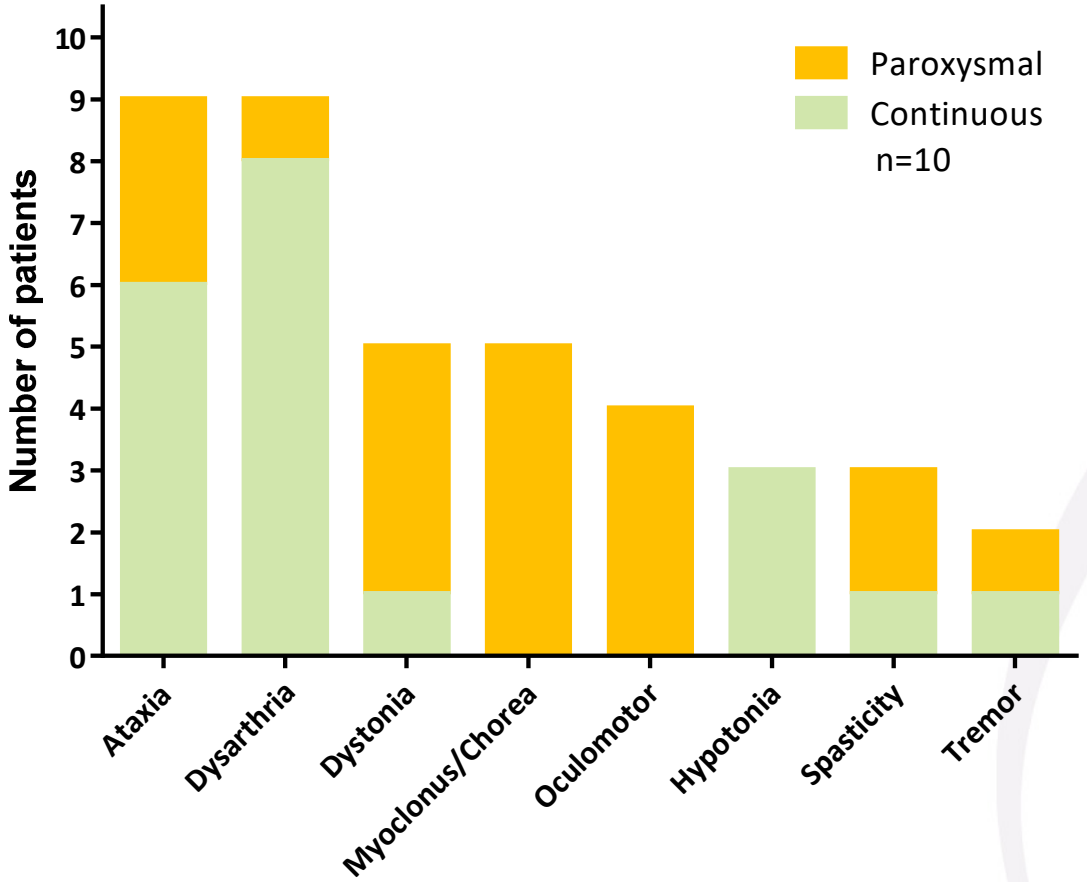
- Broad range of movement disorder symptoms reported
  - Continuous and paroxysmal
- Frequency of paroxysmal attacks is variable
- Symptom severity range from from mild-severe
  - Severe symptoms are disabling
- Fasting, exercise, infections, high temperatures, tiredness trigger paroxysmal symptoms
- Fine motor function, walking ability, physical activity, and activities of daily living affected

[1]Interviews part of Ultragenyx sponsored study UX7385 conducted by Adelphi Values

Patient/Caregiver Qualitative Study

- Glut1 DS patient/caregiver n=10
- Age range of Glut1 DS patients: 5-58 years old
- Interview
  - Please tell us about the movement disorder symptoms that are experienced
  - How do these movement disorders affect activities of daily life?
  - Are there any things that are difficult to do because of movement disorder symptoms?
  - How do you deal with these impacts in day to day life?

Different types of movement disorder symptoms reported by patients/caregivers



Impact of movement disorders reported by patients/caregivers[1]

Physical	Daily Life	Social	Emotional
Balance/Falling	Dressing	Talking to others	Embarrassed
Coordination	Eating	Viewed differently	Frustrated
Walking	Writing	Relationships	Irritable
Posture	Independence	Avoidance of social participation	Distressed/upset
Limited mobility/activities	Attention		Lack of confidence
Fatigue			
Pain			

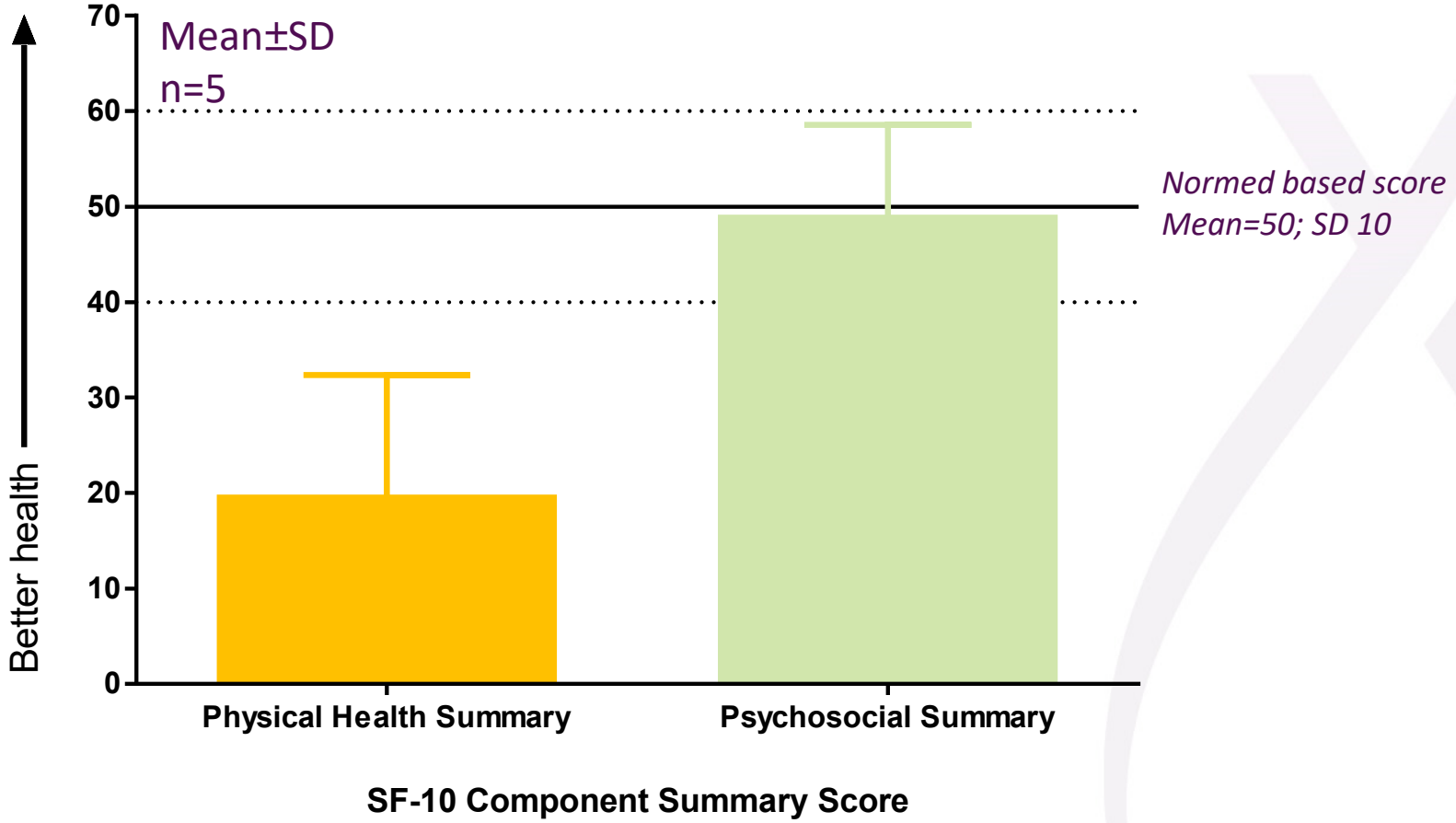
[1]Data taken from Ultragenyx sponsored study UX7385 conducted by Adelphi Values

Glut1 DS Functional Assessment Study[1]

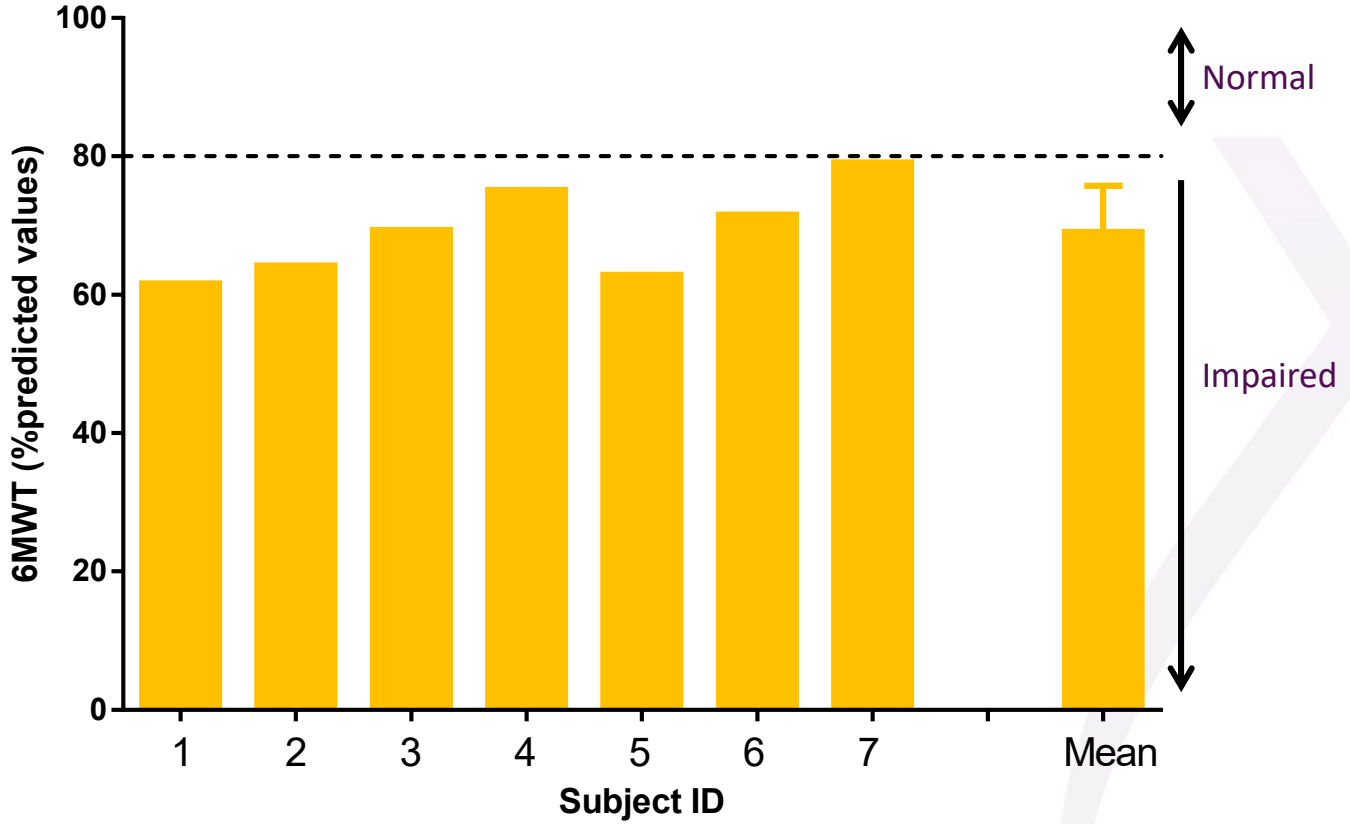
- Glut1 DS patients n=7
- Age range: 6-32 years old
- Assessments
  - HR-QoL: Medical Outcomes Survey SF-10 (5-17years old)
  - Walking capacity/endurance: 12 Minute Walk Test
  - Fine and Gross Motor Function
  - Movement Disorder Specific Rating Scales
    - Scale for the Assessment and Rating of Ataxia (SARA)
    - Abnormal Involuntary Movement Scale (AIMS)
  - Actigraphy: Activity level and sleep

[1]Ultragenyx sponsored study UX007G-CL001

Physical health is substantially impaired in children with Glut1 DS



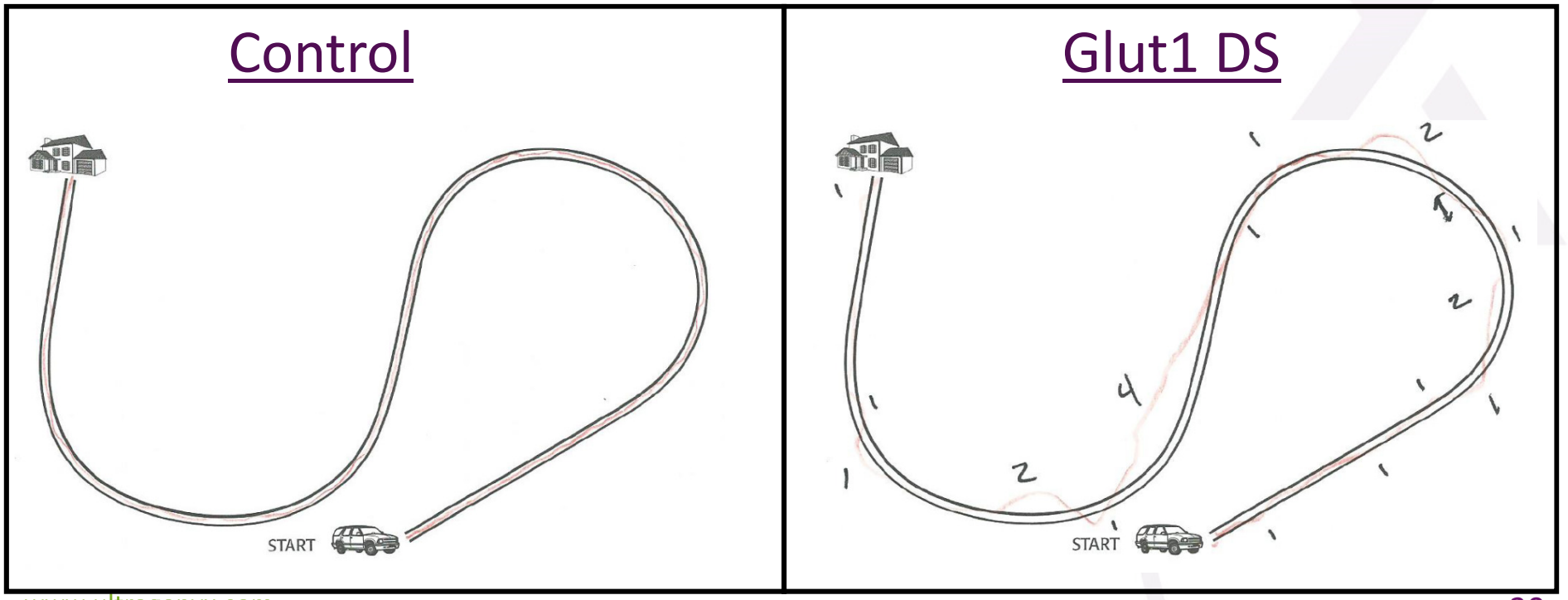
Walking capacity decreased in Glut1 DS



- No paroxysmal exertional dyskinesias were observed during testing

Fine motor precision is affected in Glut1 DS

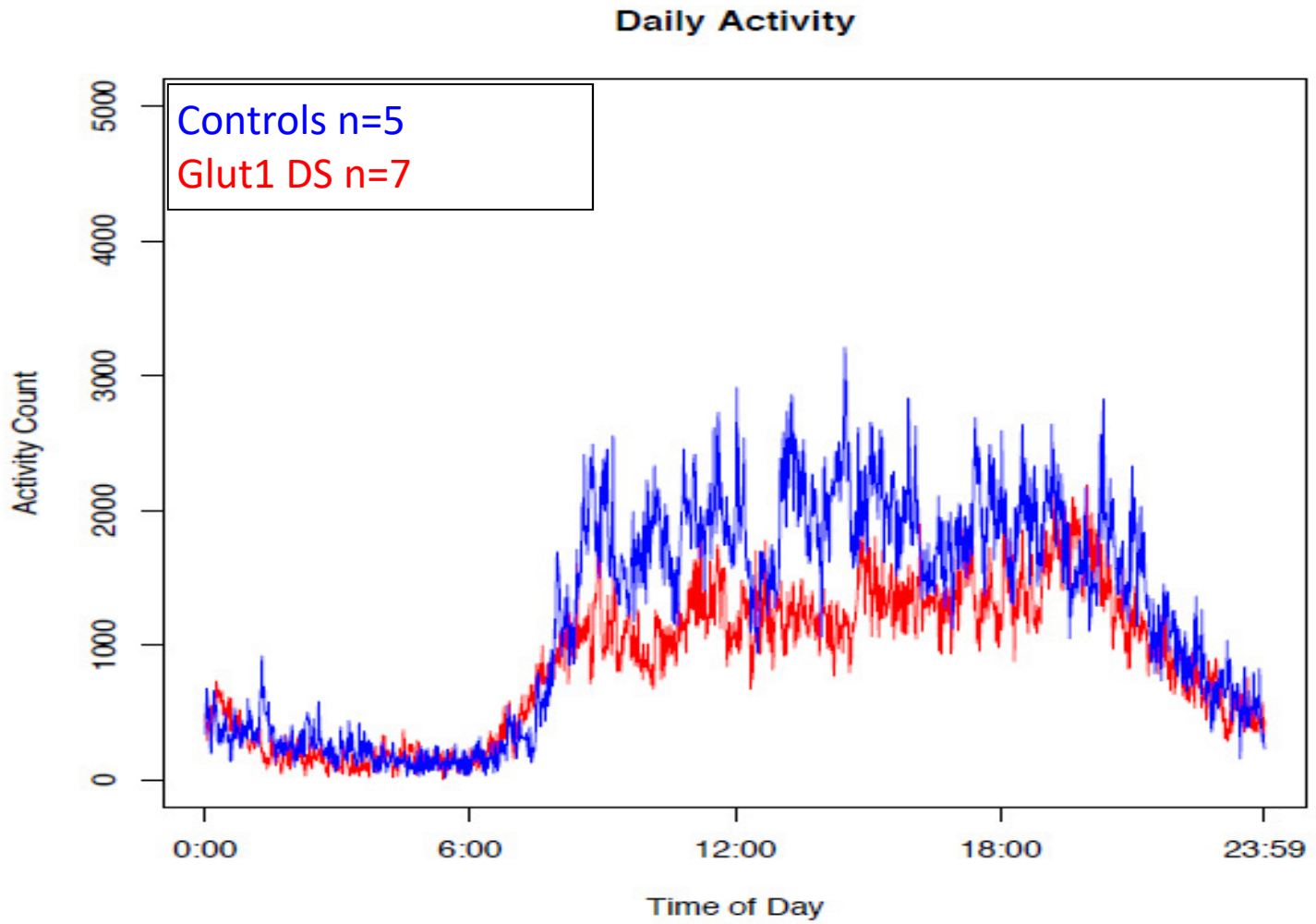
- Test evaluates precise control of hand movement
- Able to differentiate between subjects with and without impaired motor function



Limitations of movement disorder rating scales to capture paroxysmal symptoms

- Scale for the Assessment and Rating of Ataxia (SARA)
  - Maximum score = 40; higher scores = increased ataxia
    - Glut1 DS: mean SARA score 7/40
- Abnormal Involuntary Movement Scales (AIMS)
  - 10 items; 0-4 severity rating scale
  - Positive score = score ≥2 on two items or ≥3 on 1 item
  - Only 2/7 Glut1 DS patients with positive AIMS score
- Variable frequency of Glut1 DS paroxysmal movement disorder symptoms limit the use of rating scales during a clinic visit

Activity levels are reduced in Glut1 DS[1]



[1]Data taken from Ultragenyx sponsored study UX007G-CL001

Qualitative Research Findings

- Movement disorder events affect/limit physical functioning and activities of daily living
  - Paroxysmal events were not directly observed during study visit
  - In-clinic tests reflect baseline functional status
- Physical health substantially impaired in Glut1 DS
- All patients exhibited an impaired ability to walk
- Activity levels lower in Glut1 DS patients

Qualitative Research Conclusions

- Paroxysmal manifestations of Glut1 DS impact physical functioning and activities of daily living
- A daily diary is an appropriate tool to capture paroxysmal Glut1 DS events which may not present during a clinic visit
- In-clinic assessments such as walking tests can be used to assess functional capacity/energy deficiencies associated with Glut1 DS

Glut1 DS Symptom Diary: A Novel Endpoint

- How many movement disorder events did you experience that affected/limited your ability to perform everyday activities in the past 24 hours?
- Approximately how many minutes/hours did the movement disorder event last?
- Which of the following activities were affected/limited by the movement disorder event?
- Please list the symptoms you experienced during the movement disorder event

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Clinical Outcome Assessment

Selection for Glut1 DS Clinical Trials

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Glut1 DS Endpoint Model

Concept		Assessment		Endpoint
Seizure frequency	→	Seizure Diary	→	Reduction in seizure frequency
Movement Disorder frequency	→	Movement Disorder Diary	→	Reduction in movement disorder frequency
Impaired walking capacity	→	6/12 Minute Walk Test	→	Increased walk test distance
Physical Functioning/Activities of Daily Living	→	Health Related-Quality of Life questionnaire	→	Improved Health Related-Quality of Life
Self care, productivity and leisure performance	→	Canadian Occupational Performance Measure	→	Improved performance
Participation in physical activities	→	Activity Monitor	→	Increased activity levels
Cognitive function	→	Cognitive testing	→	Improved mental/motor speed, episodic memory, executive function

Glut1 DS Clinical Trials and Initiatives

- Randomized, double-blind, placebo-controlled study to assess the safety and efficacy of UX007: ***Enrollment complete; results expected end of 2016/early 2017***
- Randomized, double-blind, placebo-controlled study to assess the efficacy and safety of UX007 for movement disorders: ***Study start end of 2016***
- Open label study to assess the safety and efficacy of UX007 in combination with the ketogenic diet: ***In Development***
- Online questionnaire to further understand Glut1 DS: ***In Development***
- For more information, go to www.clinicaltrials.gov

Acknowledgements

- To the patients and families who participated in the qualitative research initiatives and clinical trials

Resources

Glut1DSinFocus.com

Glut1 DS In Focus

About Glut1 DS | Care & Support | Clinical Studies | For Health Care Professionals | About Us

Glut1 DS is a rare genetic disease.

Glucose transporter type-1 deficiency syndrome (Glut1 DS) is a rare disease that was first discovered in 1991 and is thought to affect between 3000 and 7000 people in the United States. For most, it is caused by mutations in the *SLC2A1* gene.[1,2]

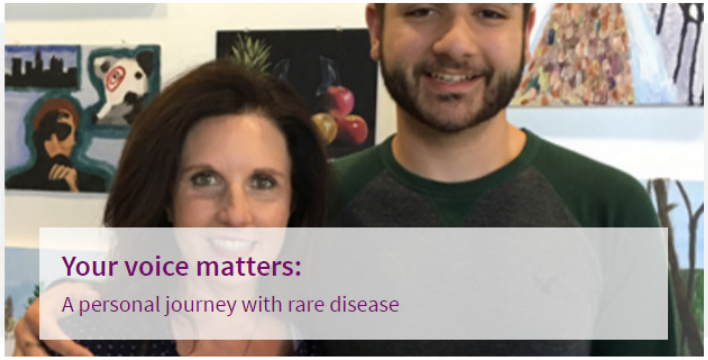
Glut1 DS In Focus is devoted to the education and awareness of Glut1 DS for patients, caregivers, and health care providers, as well as advancing research to treat this disease.

UltraRareAdvocacy.com

Patient Advocacy at ultragenyx pharmaceutical

Patient Advocacy | Patient Journeys | Resources & Learning | Events Calendar | Contact Us

With Massimiliano Barone, President of Associazione Italiana GLUT1, at the EURORDIS gala



Your voice matters:
A personal journey with rare disease

Working with and for you:
A message from our CEO

What is Patient Advocacy?

Patient advocacy serves as a point of connection between the patient community and a company or organization.

Learn More

Welcome

At Ultragenyx, the patient advocacy team is passionate about educating and supporting you: patients, families and caregivers affected by rare and ultra-rare diseases. Through this site you can find valuable resources, hear from others who live with rare diseases, and learn more about our commitment to the rare disease patient community.

Read Our Welcome Letter

Thank you!

- Contact patientadvocacy@ultragenyx.com with questions

BIOMEDIA
La condivisione del sapere

The State-and-Region Agreement asks for a declaration by Moderators, Speakers, Teachers and Tutors about the frankness of the financing sources and about their relationships with people with commercial interests within the last two years, only if there could be a conflict of interests.
The documents must be available at the Provider offices for at least 5 years.

Conflict of Interests Declaration

Undersigned Alexandra Bowden as:

□ scientific responsible □ moderator □ teacher x speaker □ tutor

of the event "**1st European Conference on Glut1 Deficiency**"
Milan - Italy, 7th-8th October 2016

Based on Art.. 3.3 about the Conflict of Interests, page 18,19 of the State-and-Region Agreement dated 19 April 2012, managed by **Biomedia n. 148**

Declares

□ that in the last two years DIDN'T have any relationships about comercial financings with people having conflict of interests in the health field

x that in the last two years HAD relationships about comercial financings with people having conflict of interests in the health field (please specify the names):

Ultragenyx Pharmaceutical Inc.

The State-and-Region Agreement asks for a declaration by Moderators, Speakers, Teachers and Tutors about the frankness of the financing sources and about their relationships with people with commercial interests within the last two years, only if there could be a conflict of interests.
The documents must be available at the Provider offices for at least 5 years.

SLIDE N.2

Undersigned

First name Alexandra Surname Bowden

Declares, under his responsibility, that in the report entitled

"Approaches to Evaluating UX007 (Triheptanoin) in Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS)"

There will be named the following Companies and / or Commercial Products:

Ultragenyx Pharmaceutical Inc.

UX007 or Triheptanoin

JUST WITH AN EDUCATIONAL AND SCIENTIFIC AIM OR TO REFER TO NATIONAL OR INTERNATIONAL GUIDELINES